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PHARMACOKINETICS OF THEOPHYLLINE INJECTIONS IN RABBITS

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ORIGINAL ARTICLE

PHARMACOKINETICS OF THEOPHYLLINE INJECTIONS IN RABBITS

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ABSTRACT

Pharmacokinetics of the theophylline injections were studied in four New Zealand rabbits, weighing 3 to 4 kg. Each rabbit received theophylline, 200 mg. as a continuous (10-minute) intravenous infusion. The pharmacokinetics of theophylline were described by a two compartment open model with first order elimination. The average of the biological half-life was 4.43 hours.

Key Words; Pharmacokinetics, theophylline, injections, rabbits.

INTRODUCTION

Theophylline is a dimethylxanthine (1) and has long been used in the therapy and treatment of reversible obstructive airway diseases (2,3). Today, theophylline is the bronchodilator of choice for treating asthma and is used as a prophylactic agent in the management of chronic asthmatic symptoms, particularly in children (3).

At present, numerous oral formulations of theophylline are available (4,5). Due to theophylline's poor solubility in water (1), aminophylline is the only salt form of theophylline (the ethylenediamine salt of theophylline) that is used for preparing small volume parenteral theophylline products. The product has some problems as its high alkaline pH, about 8.8 to 9.0, causes physical and chemical incompatibilities upon mixing with many other drugs, and also causes significant pain in some patients upon administration (3). Some patients are allergic to ethylenediamine (6).

It would be ideal to have a new small volume, concentrated (comparable to that of aminophylline, 20 mg./ml.) intravenous injectable dosage form of theophylline.

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Theophylline injection, unlike aminophylline, would contain no ethylenediamine. Such a product may be offered to those who are allergic to ethylenediamine without problem (6). Additionally, serum-level monitoring can easily be achieved, since theophylline is the active form of the drug, correlation of the administered drug and serum level is direct (7).

Therefore, a new concentrated theophylline injection has been developed on the basis of a physical-chemical approach using a ternary solvent system of ethyl lactate, ethyl alcohol, and water developed in this laboratory as the solvent for theophylline.

The pharmacokinetics of theophylline injections following constant-rate intravenous infusion were studied in rabbits. Since human and rabbit are mammals, results obtained may be expected to be projectable to humans.

MATERIALS AND METHODS

Materials

Analytical grade chemicals were obtained commercially and used without further purification. All water was deionized prior to use.

Dosage Form

Theophylline[a] injection was prepared using a mixture of 25% V/V ethyl lactate[b], 10% V/V ethyl alcohol[c], and 65% V/V water as the solvent for theophylline. The solution was brought to pH 6.5 with 1.0 N sodium hydroxide[d] and sterilized using micropore[e] filtration. The concentration of theophylline was 20 mg./ml.

Animal Experiment

All experimental work was performed using four New Zealand rabbits, weighing 3 to 4 kg. Each rabbit received theophylline, 200 mg., as a continuous 10-minute intravenous infusion[f] through a catheter[g,h] placed into its ear vein.

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[a] Theophylline anhydrous, lot 12F-0630, Sigma chemical Co., St Louis, MO 63178.

[b] Ethyl lactate, lot 3206 MH, Aldrich Chemical Co., Milwaukee, WI 53233.

[c] Ethyl alcohol U.S.P., Shell Oil Co., Corvallis, OR 97330.

[d] Sodium hydroxide, lot DEY, Mallinckrodt, Inc., St Louis, MO 63147.

[e] Acrodisc, Gelman, Ann Arbor, MI 48106.

[f] Infusion/withdrawal pump, Model 902, Harvard Apparatus Co., Millis, MA 02054.

[g] Quick-Cath 20 GO, Travenol Lab, Inc., Deerfield, IL 60015.

[h] Argyle, Brunswick Co., St Louis, MO 63103.

Blood samples were collected from an ear vein via the catheter at predetermined interval for 12 hours and analyzed for theophylline using high pressure liquid chromatography (HPLC)[i] with β-hydroxyethyltheophylline[j] as an internal standard (8,9). The mobile phase was acetonitrile[k] (7% V/V) in deionized water. The flow rate was 2.0 ml./minute. The concentrations of theophylline were quantified using a standard curve.

Standard Curve

Untreated rabbit plasma was used and known amounts of theophylline were added to produce standards of various theophylline concentrations (0.5, 1.0, 2.0, 5.0, 10.0, 20.0, 30.0, 50.0 μg/ml.) to be mixed with a constant volume of solution of acetonitrile containing internal standard (β-hydroxyethyltheophylline). These samples were analyzed by HPLC for theophylline to produce the standard curve. The peak height ratios obtained versus the known concentrations of theophylline were fitted to a straight line using linear regression (10).

Pharmacokinetics Analysis

Plasma theophylline concentrations data for each rabbit, following constant intravenous infusion, were analyzed using the computer program AUTOAN 2 (11).

RESULTS

Figure 1 shows serum concentration-time profiles following constant-rate intravenous infusion 200 mg. of theophylline in four rabbits. The pharmacokinetics of theophylline appeared to be best described by a two-compartment open model with first order elimination. A diagram of this model is shown in Figure 2.

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[i] Water Associates, Milford, MA 01757.

[j] β-hydroxyethyltheophylline, lot 60F-0308, Sigma Chemical Co., St Louis, MO 63178.

[k] Acetonitrile, lot 241091, J.T. Baker Chemical Co., Phillipsburg, NJ 08865.

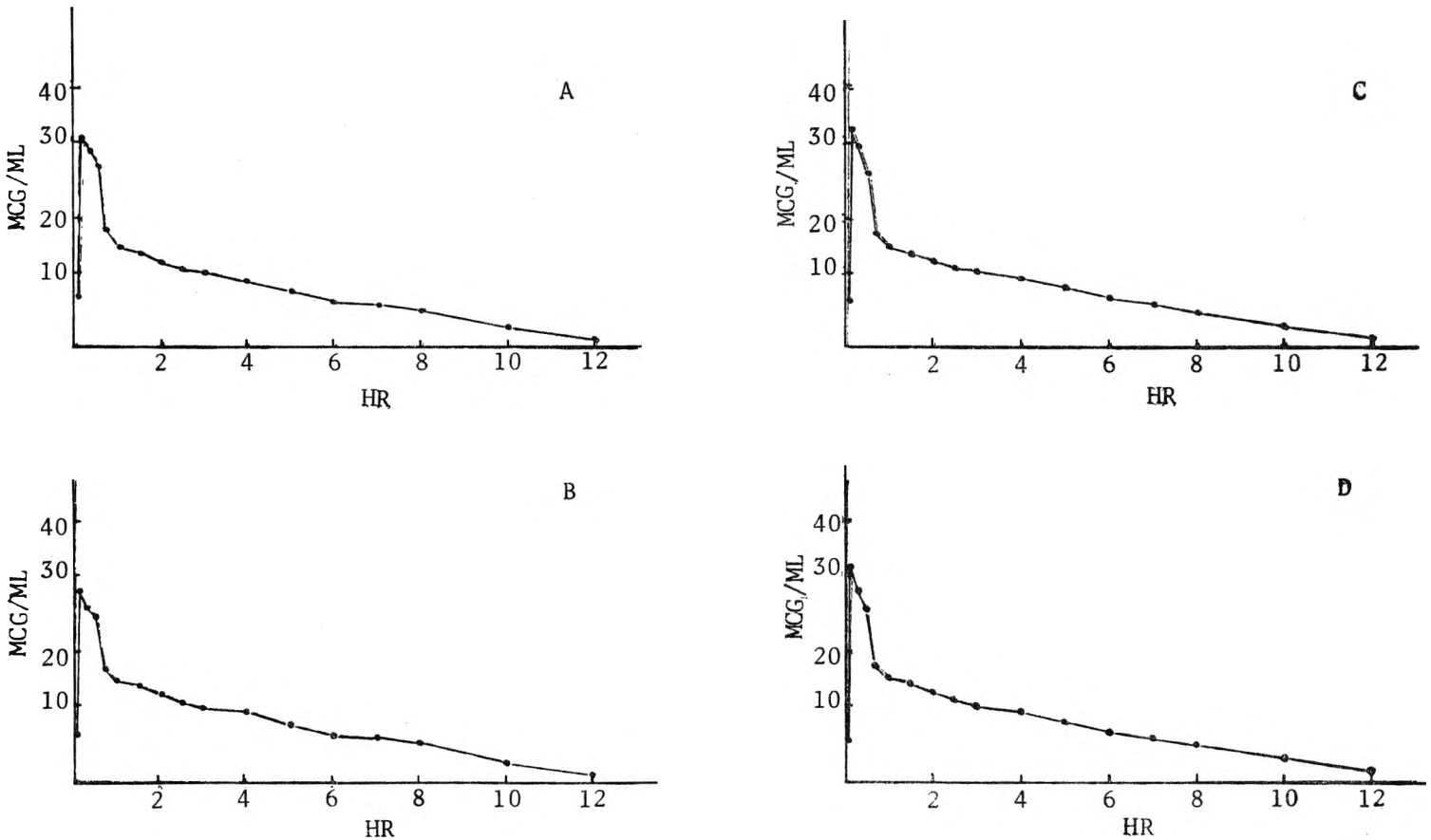
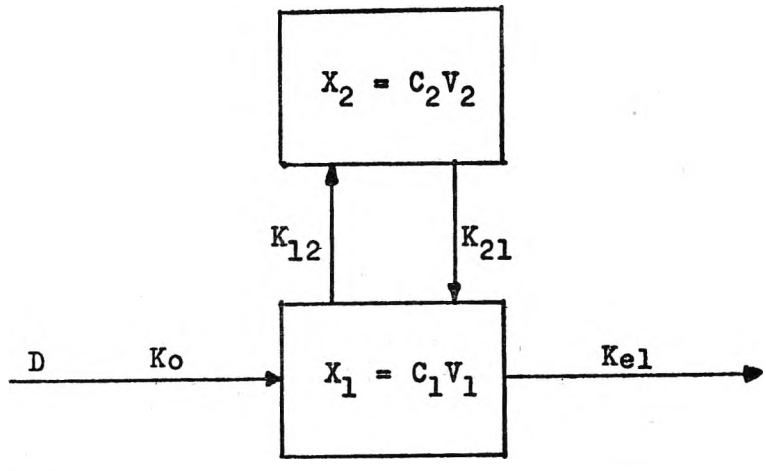


Figure 1. Serum concentration-time curves following constant-rate intravenous infusion 200 mg. of theophylline in four rabbits. A, rabbit 1, B, rabbit 2, C, rabbit 3, D, rabbit 4.



Key : D = the intravenous infusion dose.

K_0 = the zero-order infusion rate constant.

K_{12} & K_{21} = the first-order intercompartmental transfer rate constant.

Kel = the first-order elimination rate constant from the central compartment.

X_1 & X_2 = the amount of the drug in the central and peripheral compartments, respectively.

C_1 & C_2 = the serum concentration of the drug in the central and peripheral compartments, respectively.

V_1 & V_2 = the volume of distribution of the drug in the central and peripheral compartments, respectively.

Figure 2 Diagram of a two-compartment open model with constant-rate intravenous infusion input.

Table I presents the pharmacokinetic parameters, α, β, K_{12}, K_{21}, Kel, V_1 for each rabbit which obtained directly from the computer output (11), also a comparison between all these pharmacokinetic parameters and previously reported values in humans and rabbits are summarized in Table II. As can be seen some of the pharmacokinetic parameters, (α,β, K_{21}) obtained from the present study are close to those of at least one human study (21).

Table I Summary of Pharmacokinetic Parameters Obtained from Rabbits Following Constant Intravenous Infusion of Theophylline, 200 mg.

Rabbit No.	Weight (kg.)	Dose (mg./kg.)	V_1 (l/kg.)	α ($hr.^{-1}$)	β ($hr.^{-1}$)	K_{12} ($hr.^{-1}$)	K_{21} ($hr.^{-1}$)	Kel ($hr.^{-1}$)	$t_{\frac{1}{2}}$[1] (hr.)
1	3.00	66.67	2.1505	2.6751	0.1566	1.2140	1.2940	0.3237	4.4253
2	3.75	53.33	1.6667	2.4115	0.1792	1.0125	1.2256	0.3526	3.8672
3	3.50	57.14	1.7316	2.2397	0.1394	0.9996	1.0941	0.2854	4.9713
4	4.00	50.00	1.4707	2.9863	0.1501	1.3497	1.4848	0.3019	5.8824
Mean	3.31	56.78	1.7549	2.5782	0.1563	1.1440	1.2746	0.3159	4.4338[2]
S.D.	0.90	7.21	0.2861	0.3257	0.0168	0.1687	0.1628	0.0291	–

[1] $t_{\frac{1}{2}} = 0.693/\beta$

[2] Average $t_{\frac{1}{2}}$ = 0.693/average β values

Table II Comparison of Pharmacokinetic Parameters Obtained in the Present Study with Previously Published Values.

Reference	Subjects	V_1 (1/kg.)	α ($hr.^{-1}$)	β ($hr.^{-1}$)	K_{12} ($hr.^{-1}$)	K_{21} ($hr.^{-1}$)	Kel ($hr.^{-1}$)	$t_{\frac{1}{2}}$ (hr.)
Present study	Rabbits	1.7549	2.5782	0.1563	1.1440	1.2746	0.3159	4.43
Chrzanoski et al[a]	Humans	0.2310	1.5100	0.0629	0.8100	0.1560	0.6070	11.02
Mitenko & Ogilvie[b]	Humans	0.3000	5.8100	0.1590	2.7130	2.9420	0.3140	4.36
El-yazigi et al[c]	Rabbits	0.4030	4.3900	0.1790	1.7400	2.5100	0.3270	4.40
Ng & Locock[d]	Rabbits	0.2860	7.2270	0.1320	3.3860	3.7180	0.2420	5.46
Mitenko & Ogilvie[e]	Humans	0.1450	7.110	0.1560	4.7200	1.9900	0.5550	4.44
Mitenko & Ogilvie[f]	Humans	0.3440	2.5700	0.1090	0.7130	1.8080	0.1550	6.36

[a] Ref. 12
[b] Ref. 13
[c] Ref. 14
[d] Ref. 19
[e] Ref. 20
[f] Ref. 21

DISCUSSION

The pharmacokinetics of theophylline following constant rate intravenous infusion in rabbits was best described by a two compartment open model with first order elimination (12–14). As seen, after the infusion was stopped, theophylline concentrations in plasma initially decreased rapidly and then more slowly (Figures 1,2).

The biexponential equation is the solution for this model (15,16)

$$Cp\ (post) = \frac{A(1-e^{-\alpha\tau})e^{\alpha t^*}}{\alpha\tau} + \frac{B(1-e^{-\beta\tau})e^{-\beta t^*}}{\beta\tau} \quad \text{....(Eq1)}$$

or $$Cp\ (post) = A^* e^{-\alpha t^*} + B^* e^{-\beta t^*} \quad \text{....(Eq2)}$$

where, Cp (post) is the post infusion plasma concentration; A^* and B^* are definable from Eq 1 (concentration intercepts of the exponential terms at $t^* = o$); α and β are the rate constants for the distribution and elimination, respectively. t^* is the time after the end of the infusion (i.e.,$t^* = t-\tau$, where τ is the infusion time); A and B are the hypothetical intercepts with the ordinate for an intravenous bolus injection of the same amount of drug (i.e., $\tau = o$). It is evident that A and B are equal to A^* and B^* if τ is very short but the difference increases as the infusion time increases (16).

The biological half-life of theophylline in rabbit was calculated from the average elimination rate constant (β) and found to be 4.43 hours. As reported previously, the ability to detect a linear β phase was improved by extending the sampling time (12). Also, the frequency of sampling during the first hour was essential in selecting the appropriate model in order to correctly describe the pharmacokinetics of the intravenously administered drug (11). The premature termination of pharmacokinetic studies may lead to errorneous underestimated of the half-life of the drug (17).

No serious side effects or indications of theophylline intoxication were observed throughout the study. No attempt was made to calculate the relationship between the intensity of effect on pulmonary function and the amount of theophylline in the central or the peripheral compartment.

The Pharmacokinetic parameters obtained from this study were compared to previously published values for humans and rabbits. The comparison made in Table II indicate that there have been a wide variety of these values for theophylline reported in humans and rabbits. It is not surprising that these differences exist, since theophylline metabolism and elimination have wide differences in individual (18). Additionally, differences in total body fat content among subjects might contribute to the wide variation in the distribution phase of theophylline (19) as well as study design.

It is interesting that some of the pharmacokinetic parameters (α,β,K_{21}) obtained from rabbit data are close to those of at least one human study (21). The similarities among these values in rabbits and humans indicate that rabbits may be representative as in vivo models for determining pharmacokinetics of drug product containing theophylline. The absence of side effects suggests evidence for the usefulness of the dosage form developed as a new formulation for theophylline.

CONCLUSION

Pharmacokinetics of a new concentrated theophylline injection was studied in rabbits. The product developed appears to be a good candidate for future studies and may be a valuable therapeutic tool in the future.

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บทคัดย่อ

การศึกษาเภสัชจลนศาสตร์ของยาฉีดทีโอฟีลลิน (theophyllin injections) ในกระต่าย 4 ตัว ซึ่งมีน้ำหนักอยู่ระหว่าง 3–4 กิโลกรัม กระต่ายแต่ละตัวได้รับยาทีโอฟีลลินจำนวน 200 มิลลิกรัม ด้วยวิธีการฉีดแบบต่อเนื่องนาน 10 นาที ผลการศึกษาสรุปได้ว่าเภสัชจลนศาสตร์ของทีโอฟีลลินในกระต่ายเป็นแบบ two compartment open model with first order elimination และมีค่าเฉลี่ยฮาล์ฟไลฟ์ ($t_{\frac{1}{2}}$) ของทีโอฟีลลิน = 4.43 ชั่วโมง